# A Teenager with Hypogammaglobulinemia and New Pulmonary Nodules

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Case presentation: Sahar Al Baroudi, MD

Discussant: Dennis C. Stokes, MD, MPH

# Case presentation

- An 18 year old female with a past medical history of hypogammaglobulinemia and protein-losing enteropathy, who was admitted for abdominal pain and hematochezia
- One week into her hospitalization, she developed acute respiratory distress requiring up to 1.5 lpm nasal cannula of supplemental oxygen. Pulmonary service was consulted

# Case presentation

- Past Medical History:
  - Previously healthy until 15 years old
  - Protein-losing enteropathy (diagnosed March 2015)
  - Benign brain lesion  (diagnosed February 2016)
  - Hypogammaglobulinemia (diagnosed March 2016)
  - Other diagnoses: autoimmune hepatitis, iron deficiency anemia, hypothyroidism, anxiety

# Case presentation

- Family History:
  - Negative for asthma or other lung diseases
- Social History:
  - Left college due to illness
- Review of Systems:
  - Developed dyspnea with activity during this admission
- Allergies:
  - Amoxicillin – rash

# Case presentation

- Medications at time of consult:
  - Hypogammaglobulinemia
    - Immune Globulin (IVIG) 15g IV on Tues and Thurs
  - Hypothyroidism
    - Levothyroxine
  - Vitamin D Deficiency
    - Cholecalciferol
  - Anxiety
    - Sertraline
  - Protein-losing enteropathy
    - Azathioprine
    - Prednisone 10 mg daily
    - Octreotide
    - Total parenteral nutrition (TPN)
  - Nausea
    - Promethazine
    - Dronabinol
    - Ondansetron PRN
  - Abdominal pain
    - Clonidine patch
    - Hydromorphone

# Case presentation

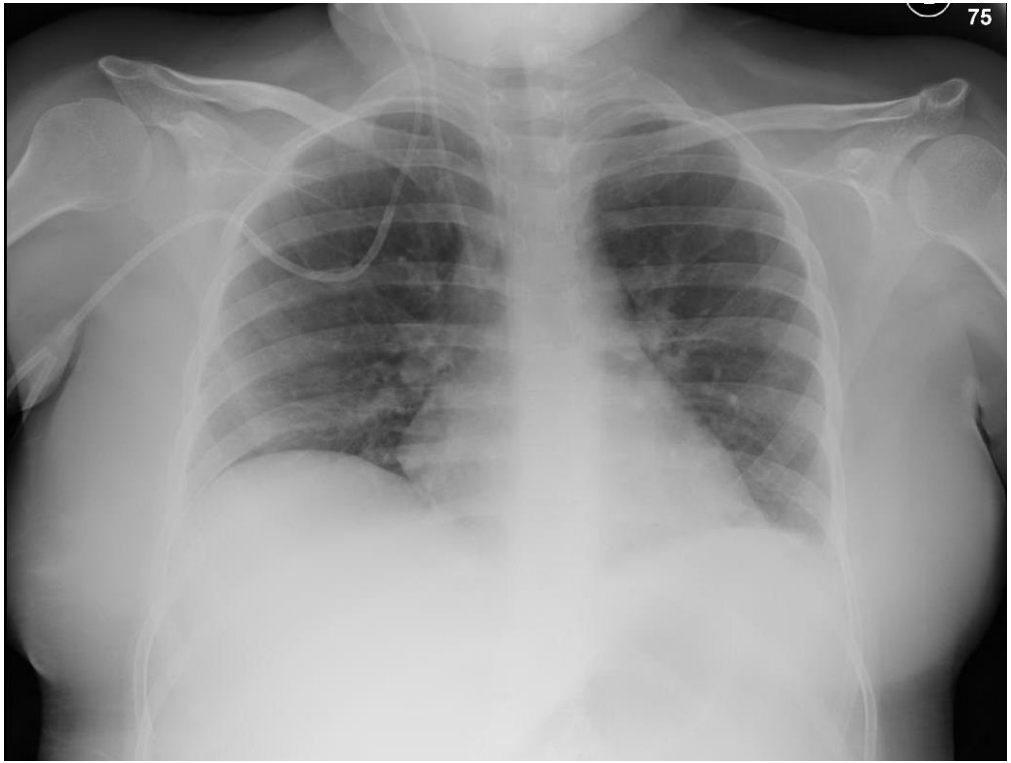
- Physical Exam:
  - T 37C, HR 122, BP 107/65, RR 26, O2 Sat 94% on 1.5 LPM NC
  - General: No acute distress
  - Lungs: **(+) Tachypnea.** No grunting, flaring, or retractions were present. Auscultation revealed clear breath sounds. **(+) Bibasilar diminished aeration**
  - Heart: Regular rate and rhythm, normal S1/S2, no murmurs
  - Abdomen: Normoactive bowel sounds. **(+) Diffusely tender.** Soft, non-distended
  - Extremities: No clubbing, cyanosis or edema.
  - Neurology: Unremarkable

# Case presentation

- Most recent laboratory studies at time of consult:
  - VBG: pH 7.35/ **pCO2 48**/ bicarb 25
  - CBC: WBC **9.4/HgB 6.2/Hct 29.9**/Plts 398k
  - CMP: Na 138/ K 3.7/ Cl 102/ Bicarb 21/ BUN 12/ Cr 0.5/ Gluc 86/ Prot 4.7/ Alb 2.4
  - IgG 1250 (N), **pre-transfusion IgG 355 (L)**
  - **IgA 25 (L), IgM 16 (L)**
  - CD3+ 87.6% (H), CD4+ 55% (H), **Absolute CD4+ 513 (L)**, CD8+ 32.4% (N), CD4/CD8 1.7

# Case presentation

- Chest radiograph one week after admission:



# Audience response question 1

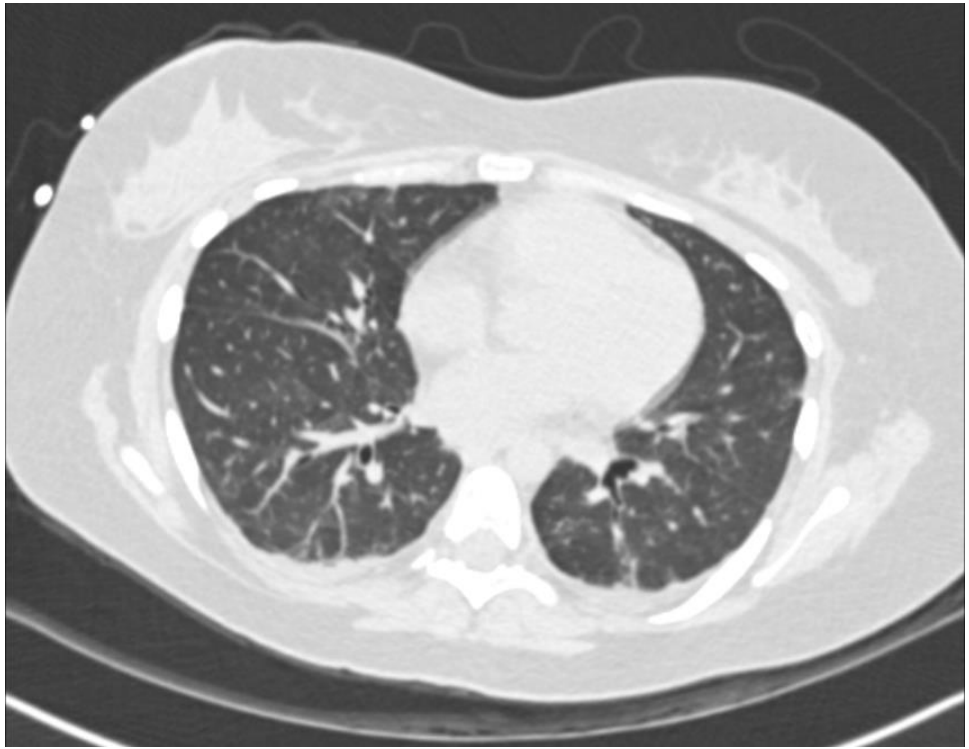
- ***Next step?***
  - *1)  Bronchoscopy with BAL*
  - *2) Bronchoscopy with transbronchial lung biopsy*
  - *3) Open lung biopsy*
  - *4) Empiric broad spectrum antimicrobial coverage and wait to see if she improves*
  - *5) Chest CT scan*

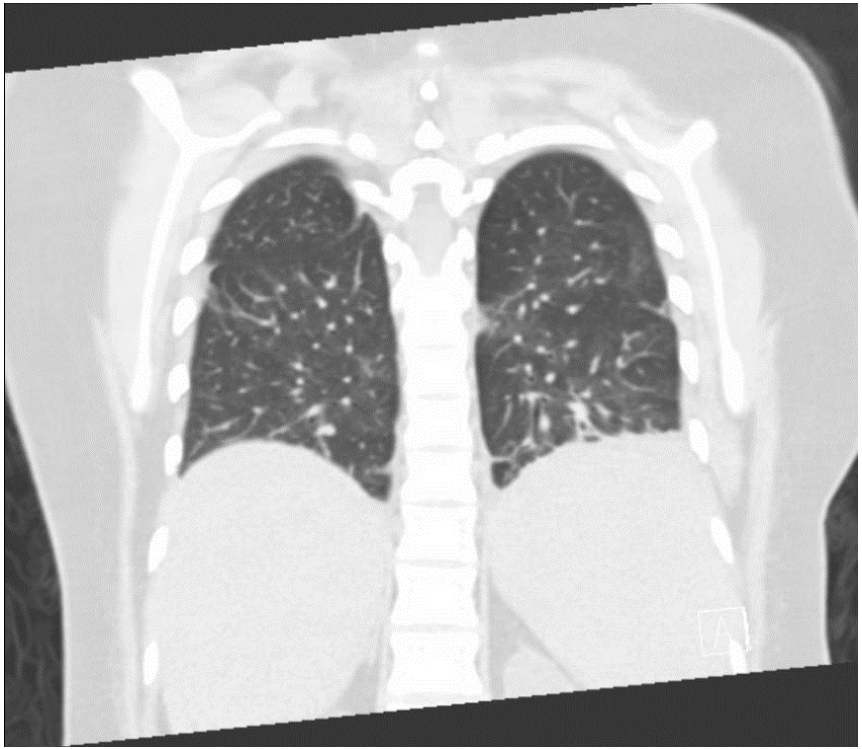
# Audience response question 1

- ***Next step?***
  - *1)  Bronchoscopy with BAL*
  - *2) Bronchoscopy with transbronchial lung biopsy*
  - *3) Open lung biopsy*
  - *4) Empiric broad spectrum antimicrobial coverage*
  - ***5) Chest CT scan***

# Case presentation

- Chest CT scan with/without contrast





Bilateral nodular consolidations and patchy ground-glass opacities

# Case discussion

- Dr. Stokes: diagnostic approach

# Diagnostic approach to the immunocompromised host with an unknown pulmonary process: “pneumopathy X”


Dennis C. Stokes MD MPH

St. Jude Children’s Research Hospital Professor of Pediatrics (Pulmonology)

University of Tennessee Health Science Center

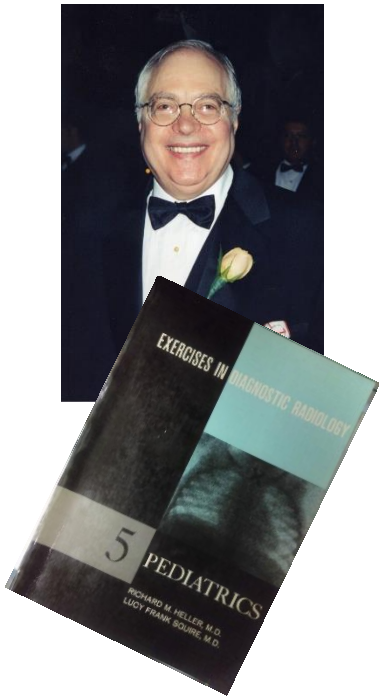

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

LeBonheur Children’s Hospital

# Dr. Helen Taussig: Final Meeting Harriet Lane Home Amphitheatre 1974

# My approach

- Team sport (Radiology, ID, A/I, Surgery)
- Likely diagnoses based on host immune defect
- Review radiology
  - Special thanks to Dr. Dick Heller
- Make sure the non-invasive “t’s” are crossed
  - Sputum, including induced sputum
  - Rapid antigen testing, blood work
- Invasive diagnostic studies
  - Bronchoscopy
  - Lung biopsy



# Differential dx based on underlying host defect

- Primary immunodeficiency
  - CGD: Aspergillus spp, Staph, *B. cepacia*
  - CVID: preRx: encapsulated organisms PostAbRx: Staph, fungi, viral
- Secondary/acquired immunodeficiency
  - Neutropenia: *H. flu*, *S. pneumoniae*, Staph, Klebsiella
  - Immunosuppressive therapies, e.g. cancer therapies
    - Bacterial: Staph
    - Fungal: Aspergillus spp.,Mucor spp, Histoplasmosis
    - Viral: CMV, PCP, VZV, HSV, RSV, hMPV

# Differential dx based on underlying host defect

- HSCT
  - Early (<30 days): Pseudomonas other bacterial, Candida spp
  - Late (>30 days): Staph, Aspergillus spp, CMV, toxo, PCP, EBV, adenovirus, RSV
  - >100 days:  Encapsulated Gram pos, VZV
- Post HSCT non-infectious complications
  - Edema
  - VOD
  - DAH
  - Idiopathic pneumonia
  - GVHD
  - Interstitial lung disease
  - PTLD
  - OB
  - COP

# Radiology

- Limited specificity to radiographic patterns
- **Airspace consolidation**
  - Hospital/community acquired pneumonias
  - Fungal pneumonia
  - Aspiration
  - Idiopathic pneumonia syndrome
  - Tb/atypical Tb
  - DAH
  - ARDS
  - Pulmonary edema
  - TRALI: transfusion related acute lung injury

# Radiology

- **Nodular lesions**
- Discrete
  - Fungal infection
  - Nocardia
  - Metastatic calcifications
  - PTLD: post transplant lymphoproliferative disease
  - Malignancy
  - Septic emboli
- Tree-in-bud pattern
  - Viral pneumonia
  - Bacterial pneumonia
  - BOS

# Radiology

- **Ground glass opacities**
  - Pulmonary edema
  - TRALI
  - ARDS
  - DAH
  - CMV
  - PCP
  - Viral: CMV, Respiratory (RSV, hMPV, parainfluenza, adenovirus)
  - Drug injury

# Radiology: CT versus plain radiography

- CT more sensitive to extent of lung change
- May show secondary findings: early cavitary change, pleural effusions,  splenic fungal lesions
- Helps plan invasive diagnostic studies: bronchoscopy/BAL, TBB, needle aspiration biopsy
- In suspected BOS,  HRCT with inspiratory/expiratory view may be sufficient to avoid open lung biopsy

# Non-invasive testing

- Sputum: induced, or after intubation
- Rapid viral panels: RSV, influenza, parainfluenza, Chlamydia
- Serum galactomanan for Aspergillus
- Urinary antigen, serum antibodies for Histoplasmosis
- Genetic probes: *P. jirovecii*, *Legionella*, *Mycoplasma pneumoniae*

# Bronchoscopy

- Indications:
  - Failure to clear with appropriate empiric therapy
  - Suspicion of endobronchial obstruction (infection, tumor)
  - Recurrent pneumonia in lobe or segment
  - Suspicion of opportunistic infection (e.g. *P. jirovecii*)

# Bronchoscopy

- Broncho-alveolar lavage
- Bronchoscopic biopsy techniques
  - Mucosal biopsy
  - “Blind” transbronchial biopsy
  - “Guided” biopsy: EBUS, CT-guided/navigational methods
- Limitations
  - Limited availability of “guided” techniques in pediatrics
    - Potential application to pulmonary nodular disease
    - ? Less risk than IR CT guided needle aspiration biopsy
- What is the value of a “negative” bronchoscopy
  - Narrowing/discontinuing antimicrobial coverage
  - Fungal pneumonias: yield lowest when done early
  - May be improved by galactomannan detection BAL

# Lung biopsy

- IR:  CT-guided needle aspiration biopsy
  - Risk of hemorrhage, pneumothorax, non-diagnostic biopsy
- Open lung biopsy
  - Thoracotomy
  - Thoracoscopic biopsy (VATS)

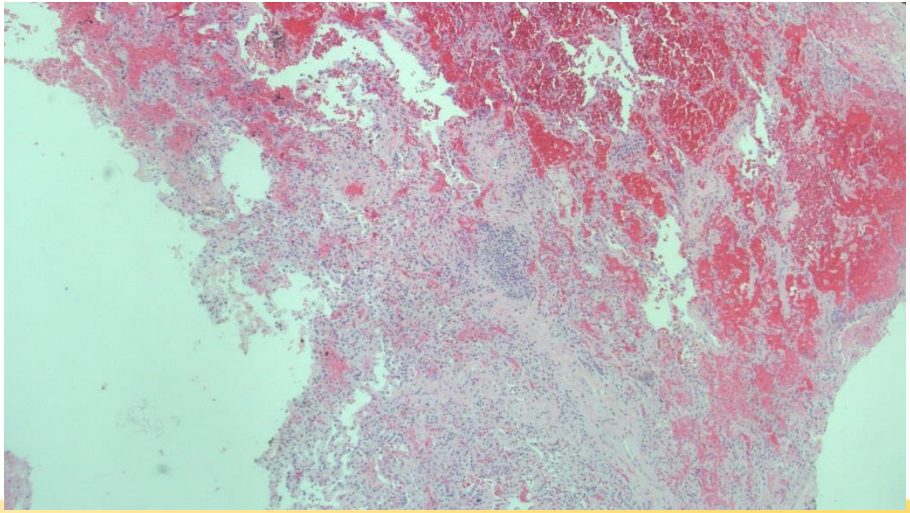
  - NOW BACK TO THE CASE….

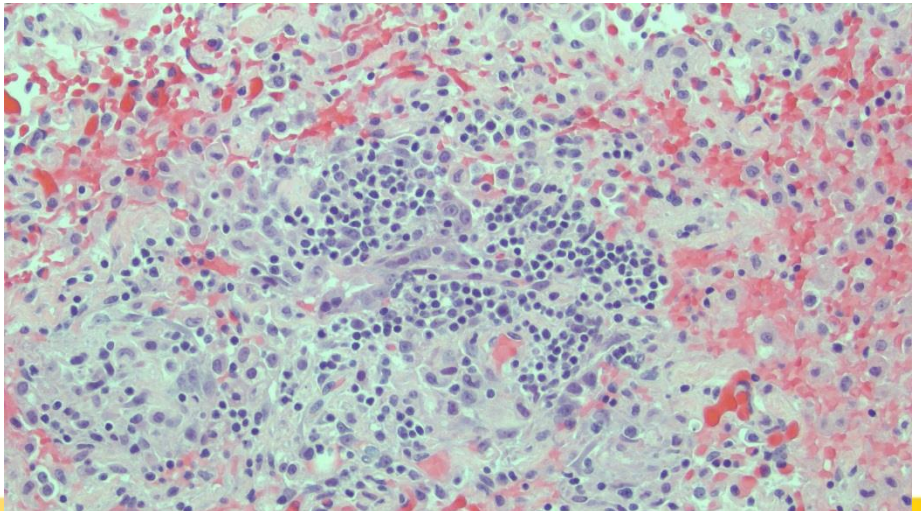
# Case presentation

- She subsequently developed a fever, and was treated for presumed bacterial pneumonia with a 14 day course of cefepime, and was started on prophylactic pentamidine
- However, her fever did not improve on antibiotics, and an inflammatory process was suspected

# Case presentation

- Bronchoscopy with BAL and other infectious work-up were negative
- Nodule biopsy via VATS with RUL wedge resection showed necrotic and chronic inflammation pathology





# Case presentation

- Hospital course after lung biopsy:
  - Respiratory
    - Supplemental oxygen requirement increased to 4 LPM via nasal cannula
  - GI
    - Stool output improved; were able to decrease dose of IVIG
  - Immunology
    - IgG levels remained stable on smaller dose of IVIG
  - ID
    - Fever resolved; no new growth from bronchoscopy alveolar lavage
  - Neurologic
    - Mental status intact, brain lesion unchanged on repeat imaging
  - Endocrine
    - Stable on levothyroxine

# Common variable immunodeficiency (CVID)

- Most common primary immunodeficiency
  - Prevalence: 1:25,000-1:30,000
- Definition (ESID, 2014):
  - Age > 4
- At least one:
  - Increased susceptibility to infection
  - Autoimmune disease
  - Granulomatous disease
  - Unexplained polyclonal lymphoproliferation
  - Affected family member with Ab deficiency
- AND
  - Marked decrease IgG, IgA (with or w/o low IgM)
    - Poor functional Ab response

# Common variable immunodeficiency (CVID)

- AND
  - Secondary causes of hypogammaglobulinemia ruled out
- AND
  - no evidence of profound T-cell deficiency

# Common variable immunodeficiency (CVID)

- Chronic and recurrent infections in 32 children with CVID
  - Bronchitis 88%
  - Pneumonia 78%
  - Sinusitis 78%
  - OM 69%
  - Fungal infections (including skin) 47%
  - GI infections 34%
  - Skin infections 22%
  - Parasites 16%
  - Conjunctivitis 9%
  - Oral infections 9%

Urschel, S et al J. Pediatr 2009;154:888

# Common variable immunodeficiency (CVID)

- Noninfectious pulmonary disease
  - More common in adolescence, young adulthood
  - “Granulomatous-lymphocytic interstitial lung disease”
    - Granulomatous lung disease
    - Lymphocytic interstitial lung disease (LIP)
    - Follicular bronchiolitis
    - Lymphoid hypeplasia
- Risk of progression to B-cell lymphomas

Ambruso, DR, Johnston, RB Primary immunodeficincy (Kendig and Chernick’s Disorders of the Respiratory Tract in Children, 8th ed, 2012

# Emerging genetic basis of CVID

- Multiple genetic disorders associated with the CVID phenotype
- Majority of familial cases appear autosomal dominant
  - *NFKB2*
  - CD19
  - TACI
  - ICOS
  - *PIK3CD* gain of function mutations
  - CTLA-4 loss of function mutations
- LATAIE: similar phenotype but autosomal recessive inheritance
  - Biallelic mutations in LRPA gene
  - "LRBA deficiency with autoantibodies, regulatory T (Treg) cell defects, autoimmune infiltration, and enteropathy"

Lo, B et al Blood 2016;128:1037

# Audience response question 2

- ***What diagnostic test would you do next?***
  - *1) Repeat lung biopsy at a more pathologic area*
  - *2) Additional targeted immunologic testing*
  - *3) Whole exome sequencing with targeted genetic testing*
  - *4) Stop antibiotics and repeat broncho-alveolar lavage off antibiotics*

# Audience response question 2

- ***What diagnostic test would you do next?***
  - *1) Repeat lung biopsy at a more pathologic area*
  - *2) Additional targeted immunologic testing*
  - ***3) Whole exome sequencing with targeted genetic testing***
  - *4) Repeat bronchoscopy alveolar lavage off antibiotics*

# Case presentation

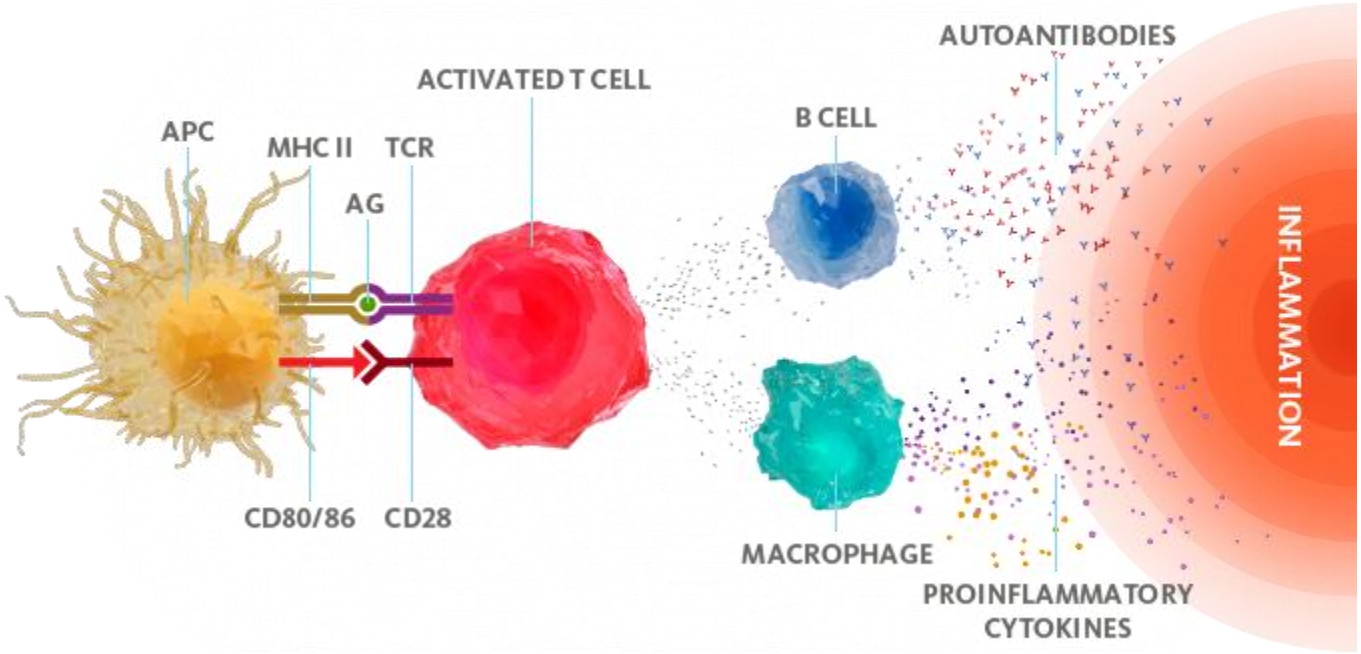
- She had whole exome sequencing that revealed a missense mutation (c.140 T>C, p.Leu47Pro) in CTLA-4 gene. This was confirmed by targeted genetic sequencing

# Case discussion

- CTLA-4 haploinsufficiency as a new model of immunodeficiency and autoimmunity

# Discussion

- Cytotoxic T-Lymphocyte associated antigen 4 (CTLA-4) sends an inhibitory signal to T-cells




NIH: The National Center for Biotechnology Information, 2016; Orencia, 2017

# Discussion

- CTLA-4: cytotoxic T lymphocyte antigen 4: critical “checkpoint” of immune response
- Ctla4 knockout mice: lethal multiorgan lymphocytic infiltration
- CHAI: syndrome of CTLA-4 haploinsufficiency with autoimmune infiltration
  - Heterozygous loss of function mutations associated with lymphocytic organ infiltrations including lung

NIH:U.S National Library of Medicine, 2016

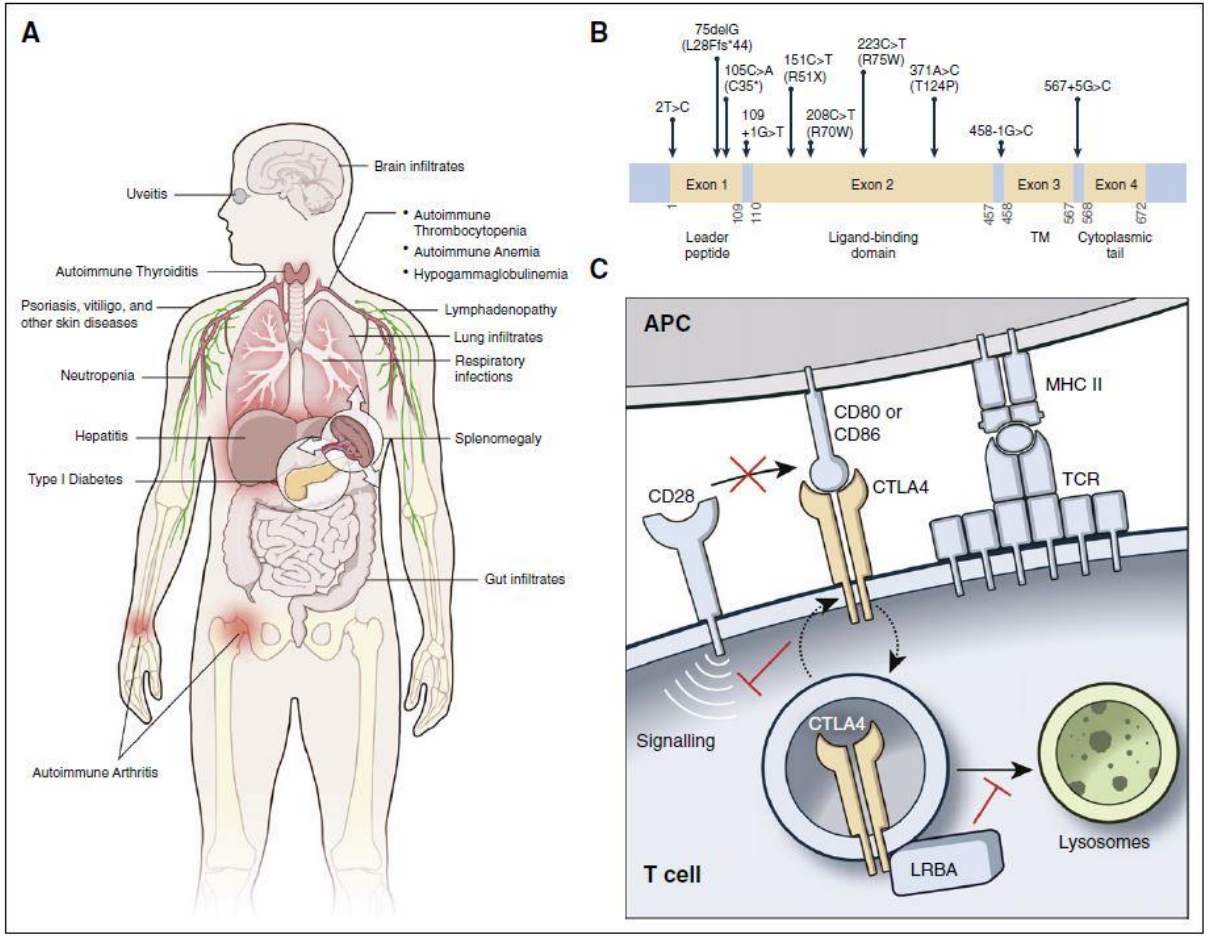
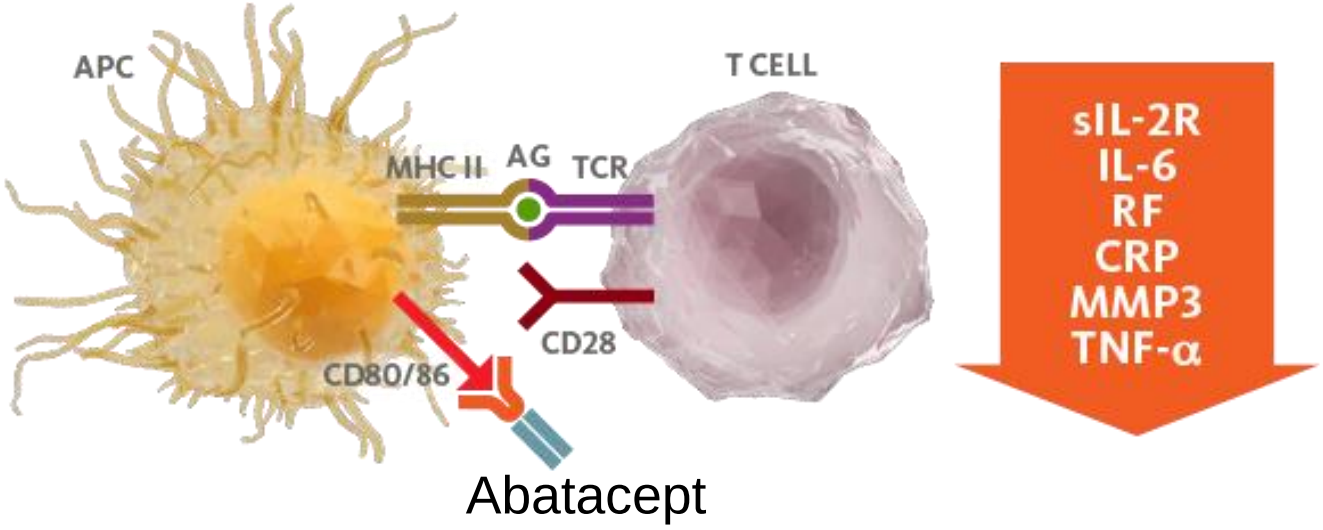



**Figure 1. CHAI and LATAIE disease phenotype and mechanism.** (A) Clinical features of CHAI and LATAIE disease. (B) Schematic of the *CTLA4* exons showing the mutations in CHAI patients. TM, transmembrane domain. A schematic displaying *LRBA* mutations causing LATAIE can be found in Lo et al,[12] Alkhairy et al,[17] and Gámez-Díaz et al.[18] (C) Model depicting the function of CTLA-4 and its regulation by LRBA.

Lo, B et al Blood 2016;128:1037

# Case presentation: treatment

- Abatacept contains Fc region of immunoglobulin attached to the CTLA-4. This can replace the CTLA-4 in providing an inhibitory signal for T-cell activation



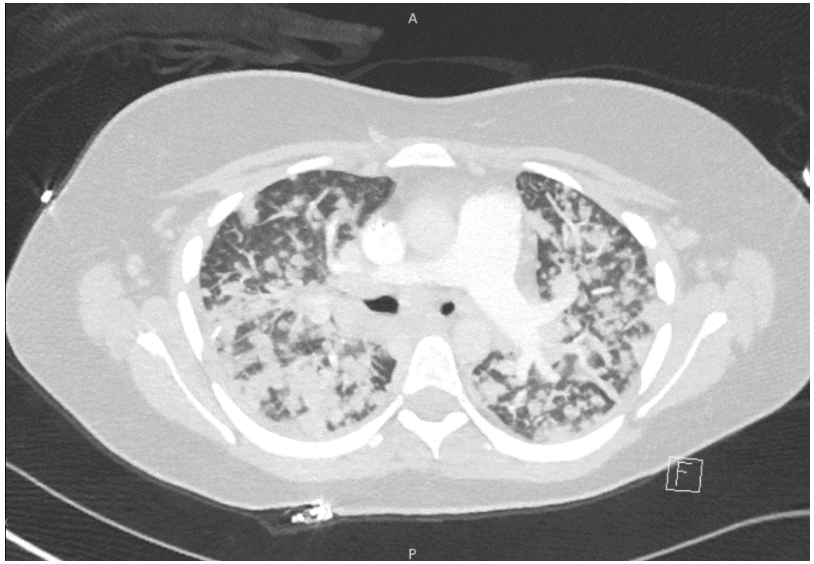

Lo et al, 2015; Orencia, 2017

# Case presentation: later course

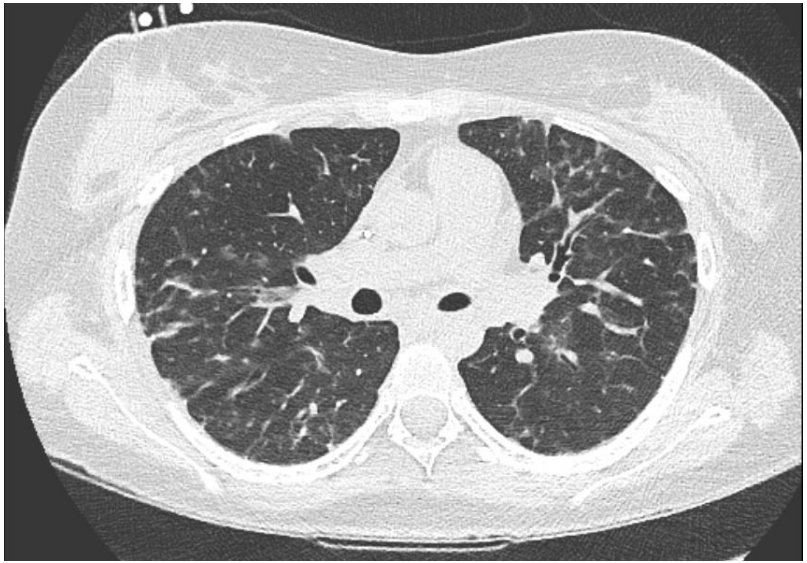
- She was treated with abatacept and sirolimus for CTLA-4 deficiency for additional immunosuppression. She was continued on IVIG due to hypogammaglobulinemia
- Her symptoms improved, and she was discharged home on supplemental oxygen 2 LPM via nasal cannula

# Case presentation

- Serial chest CT scans




One month prior to abatacept & sirolimus

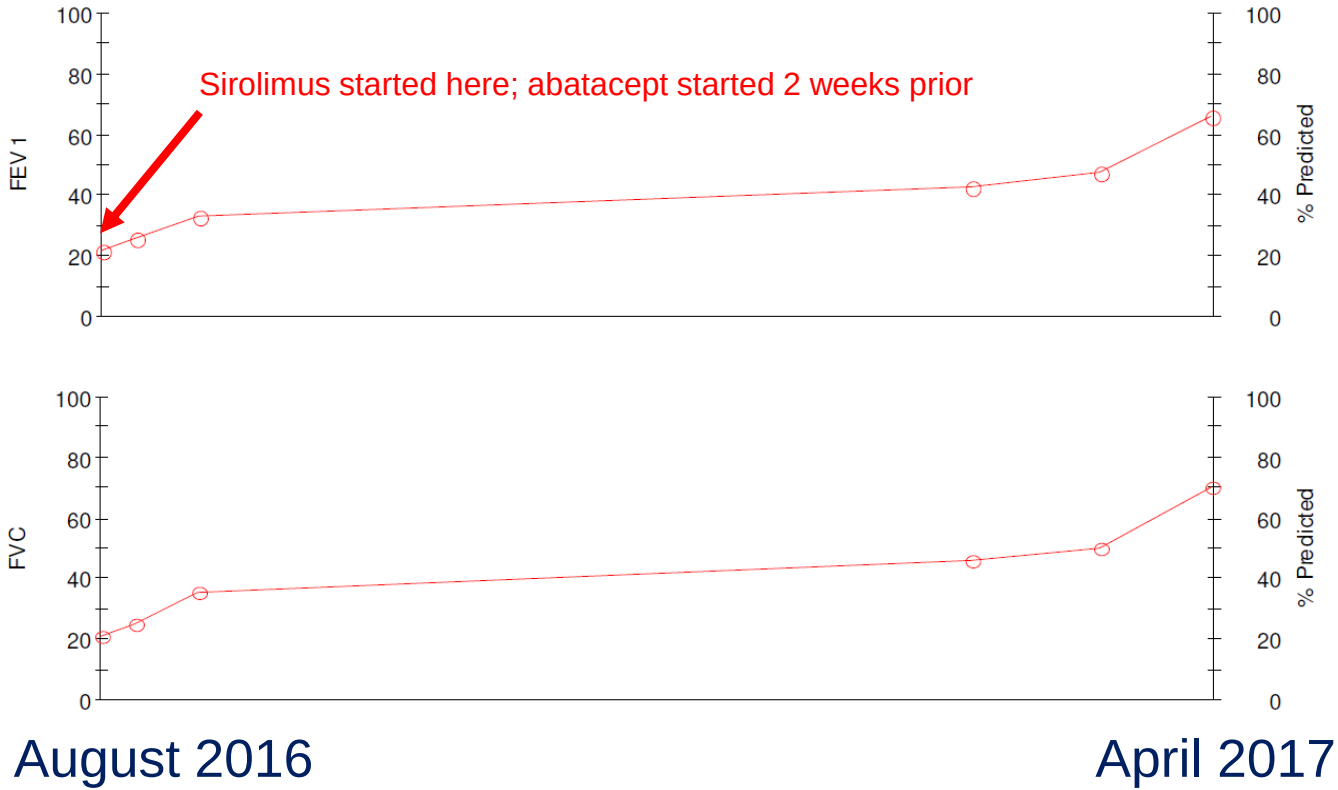


Two months post abatacept & sirolimus

# Case presentation: outpatient follow-up

- Ambulating better on room air
- Shortness of breath with walking longer than 30 minutes or going up stairs
- Albuterol used once over the past month

# Pulmonary function tests



# Case presentation: outpatient follow-up

- Immunology:
  - Continued on abatacept, sirolimus, and IVIG. Planning for bone marrow transplant
- ID:
  - Mycobacterium avium-intracellulare treatment:  Started on ethambutol, azithromycin, and rifampin for positive sputum culture
  - Pneumocystis prophylaxis: Switched from pentamidine to sulfamethoxazole-trimethoprim
- GI:
  - Continued on TPN

Questions?

# References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